

Type 1 Diabetic Drivers With and Without a History of Recurrent Hypoglycemia-Related Driving Mishaps

Physiological and performance differences during euglycemia and the induction of hypoglycemia

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OBJECTIVE— Collisions are more common among drivers with type 1 diabetes than among their nondiabetic spouses. This increased risk appears to be attributable to a subgroup of drivers with type 1 diabetes. The hypothesis tested is that this vulnerable subgroup is more at risk for hypoglycemia and its disruptive effects on driving.

RESEARCH DESIGN AND METHODS— Thirty-eight drivers with type 1 diabetes, 16 with (+history) and 22 without (−history) a recent history of recurrent hypoglycemia-related driving mishaps, drove a virtual reality driving simulator and watched a videotape of someone driving a simulator for 30-min periods. Driving and video testing occurred in a double-blind, randomized, crossover manner during euglycemia (5.5 mmol/l) and progressive hypoglycemia (3.9–2.5 mmol/l). Examiners were blind to which subjects were +/-history, whereas subjects were blind to their blood glucose levels and targets.

RESULTS— During euglycemia, +history participants reported more autonomic and neuroglycopenic symptoms ($P \leq 0.01$) and tended to require more dextrose infusion to maintain euglycemia with the same insulin infusion ($P < 0.09$). During progressive hypoglycemia, these subjects demonstrated less epinephrine release ($P = 0.02$) and greater driving impairments ($P = 0.03$).

CONCLUSIONS— Findings support the speculation that there is a subgroup of type 1 diabetic drivers more vulnerable to experiencing hypoglycemia-related driving mishaps. This increased vulnerability may be due to more symptom “noise” (more symptoms during euglycemia), making it harder to detect hypoglycemia while driving; possibly greater carbohydrate utilization, rendering them more vulnerable to experiencing hypoglycemia; less hormonal counterregulation, leading to more profound hypoglycemia; and more neuroglycopenia, rendering them more vulnerable to impaired driving.

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Worldwide driving collisions account for 1.2 million fatalities and 50 million injuries annually (1). Drivers with type 1 diabetes have more driving mishaps (2). In both Europe and the U.S. type 1 diabetic drivers have been found to have more than twice as

many collisions as their nondiabetic spouses (3) possibly because mild hypoglycemia significantly affects cognitive-motor functioning in general (4–6) and the cognitive-motor skills relevant to driving a car in particular (7,8). Severe hypoglycemia precludes safe driving and

can contribute to vehicular fatalities (9). Further, mild hypoglycemia can impair judgment as to whether or not to drive (10,11).

Just as some individuals with type 1 diabetes are more vulnerable to experiencing severe hypoglycemia (12), some individuals may be more vulnerable to hypoglycemia-related driving mishaps. This speculation is supported by the U.S.-European survey (3) in which only 27% of the type 1 diabetic drivers reported vehicular collisions in the previous 2 years (3) and a prospective study in which only 22% of the sample reported a collision during the 12-month observation (13). In a previous study of hypoglycemia and driving, we conducted post hoc analyses comparing individuals with a recent history of no driving mishaps versus individuals with a history of multiple driving mishaps (14). Those with a +history were more likely to be female ($P = 0.02$), tended to demonstrate greater carbohydrate utilization ($P = 0.07$) and less epinephrine release ($P = 0.11$), and drove significantly worse during hypoglycemia ($P = 0.01$) (14). The present study was an a priori hypothesis-testing replication comparing subjects with or without a recent history of recurrent hypoglycemia-related driving mishaps, using a similar methodology, to test whether +history type 1 diabetic drivers were 1) more vulnerable to experiencing hypoglycemia through greater carbohydrate utilization, 2) more likely to be female, 3) more vulnerable to progressive hypoglycemia because of a smaller counterregulatory epinephrine response, 4) less aware of hypoglycemia due to fewer symptoms (autonomic and neuroglycopenic) during hypoglycemia, and 5) more impaired while driving during hypoglycemia.

RESEARCH DESIGN AND METHODS

Forty-two adults with type 1 diabetes were recruited through regional advertisements. Inclusion criteria

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were that subjects 1) had type 1 diabetes for at least 1 year, 2) were between the ages of 21 and 70, 3) drove a minimum of 6,000 miles a year, and 4) either reported no driving mishaps (no collisions, citations, or automatic driving where they drove from point A to B with no recollection or someone else took over control of the vehicle due to hypoglycemia) in the past 12 months (–history group) or reported at least two such mishaps in the past 12 months (+history group). Further, because we were going to expose subjects to hypoglycemia (~2.2 mmol/l) through insulin infusion and take frequent blood samples, we excluded subjects with hematocrit <38% for men or <36% for women, the presence of an electronic pacemaker or >5% atrial or ventricular ectopy, and pregnant females. Four subjects prematurely discontinued testing: three had insufficient intravenous access for the hyperinsulinemic clamp procedure and one experienced lower extremity muscle twitching resulting from acute or chronic hypomagnesemia. The resulting sample of 38 participants had a mean age of 42.5 ± 12 years (median 42 years, range 21–66 years), disease duration of 21.6 ± 9.4 years (median 20 years, range 1–52 years), and A1C of 7.4 ± 0.8%. As illustrated in Table 1, the +/–history groups did not differ on any diabetes, hypoglycemia, or driving parameters other than +history subjects reported more episodes of severe hypoglycemia and driving mishaps in the previous 12 months.

Procedure

After signing an institutional review board–approved consent form, participants completed an outpatient screening evaluation including a medical history, physical examination, 12-lead electrocardiogram, and laboratory evaluation with A1C, complete blood count, and a comprehensive metabolic panel. They were also introduced to and rehearsed using the simulator.

For the 48 h before admission, subjects were instructed to avoid hypoglycemia by reducing total insulin by 10%, routinely testing blood glucose five times a day, and eating prophylactically 10 g of carbohydrates when blood glucose fell to <5.5 mmol/l. Intermediate and long-acting insulins were discontinued 24 and 36 h before hospitalization, respectively. During this preadmission period and hospital admission, only short- and rapid-acting insulins were used.

Table 1—Subjects' descriptive characteristics

Variables	–History	+History	P value
N	22	16	
Age (years)	42 ± 12.9	42 ± 12.8	NS
Sex (% female)	34% (7)	62% (10)	NS
Education/year	15 ± 2.6	16 ± 2.2	NS
A1C	7.1 ± 0.8	7.5 ± 0.9	NS
Diabetes duration (years)	21 ± 9.4	21 ± 10.8	NS
Insulin (units/day)	42 ± 15.5	42 ± 32.3	NS
BMI	27 ± 5.2	26 ± 4.2	Ns
Hypoglycemia awareness*	82% (18)	75% (12)	NS
Severe hypoglycemia† in past 12 months	0.5 ± 0.7	1.6 ± 2.2	<0.03
Subjective neuropathy	23% (5)	44% (7)	NS
Objective neuropathy	9% (2)	19% (3)	NS
Retinopathy	41% (9)	25% (4)	NS
Laser eye therapy	4% (1)	12% (2)	NS
Driving experience (years)	27	27	NS
Miles driven per year	18.5714 ± 12.040	17.7308 ± 16.133	NS
Self-monitored blood glucose before driving‡	1.3	1.7	NS
Fast-acting sugar in car‡	2.0	3.0	NS
No. mild hypoglycemia while driving in past 6 months	0.7	1.1	NS
No. driving mishaps in past 12 months	0	2.8	0.0001
Hypoglycemic nadir (mmol/l)	2.7 ± 0.9	2.6 ± 0.3	
Peak epinephrine during hypoglycemia	345 ± 178	217 ± 137	0.05
Self-treatment during hypoglycemic drive	59% (13)	44% (7)	NS

Data are means ± SD or % (n) unless otherwise indicated. *Hypoglycemia awareness was defined using the criteria reported by Clarke et al. (25). †Diabetes Control and Complications Trial criteria for severe hypoglycemia was used, i.e., episodes where individual was unable to treat himself or herself, either because he or she was stuporous, was unconscious, or had a seizure. ‡Mean rating on a scale where 1 is always, 2 is frequently, 3 is seldom, and 4 is never.

Subjects were admitted to the University of Virginia General Clinical Research Center at 4:00 P.M. on the evening before the hyperinsulinemic clamping procedure. Subjects were instructed on and given time to again practice driving the simulator and rating nine common symptoms of hypoglycemia on a 0–6 scale into a hand-held computer. Subjects were then provided with a standardized (50% carbohydrate, 20% protein, and 30% fat) eucaloric, caffeine-free meal at 6:00 P.M. and a bedtime snack at 9:00 P.M. Subjects were allowed glucose-free, caffeine-free drinks throughout the evening and retired at 11:00 P.M. Subjects were not allowed to eat any additional food during hospitalization other than that provided by the General Clinical Research Center or that required to treat blood glucose <5.5 mmol/l. Two intravenous lines were placed in the nondominant hand and arm for overnight infusion of insulin and hourly blood sampling to maintain glucose between 5.6 and 8.3 mmol/l.

On the first morning of testing, subjects were awakened at ~7:00 A.M. and given time to freshen up. They remained fasting until after the study procedures were completed. Immediately before testing, an additional retrograde hand intravenous line was inserted. Activated charcoal packets were affixed over this intravenous area for arterialized sampling of blood glucose every 5 min and epinephrine every 10 min (15). Euglycemia, with a plasma glucose goal of 6.1 mmol/l (110 mg/dl), was achieved and maintained using variable 20% dextrose infusion (16). After glucose and insulin stabilization, subjects performed 30 min of testing. Subsequently, dextrose infusion was slowed or discontinued to ensure a steady descent into hypoglycemia at a blood glucose rate of fall of 0.055 mmol/l/min. Progressive hypoglycemia testing began when blood glucose reached 3.9 mmol/l (70 mg/dl) and ended 30 min later at a blood glucose nadir of 2.5 mmol/l (45 mg/dl) (16). Progressive hypoglycemia,

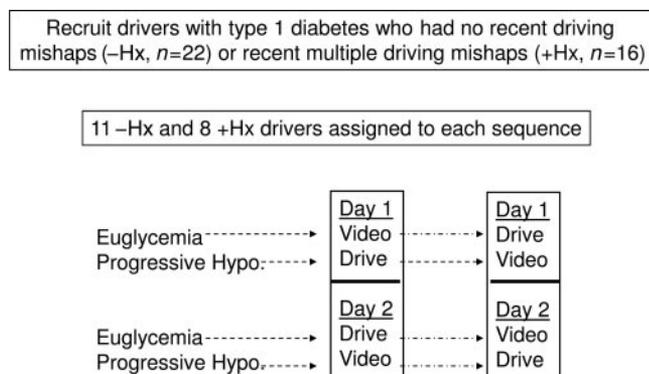


Figure 1—Randomized, crossover design controlling for practice and antecedent hypoglycemia effects influencing condition effects. Hx, history; Hypo, hypoglycemia.

rather than the traditional hypoglycemia clamp (4,5), was used because it was thought to be more similar to real-world conditions. Euglycemia testing always preceded hypoglycemia testing to avoid the affect of any lingering neuroglycopenia on performance during euglycemia. The same procedures were followed on the second day of testing. Testing was done on 2 consecutive days to avoid losing subjects due to rescheduling a second hospitalization. Figure 1 depicts the randomized crossover research design. Hypoglycemic driving was equally as likely to occur on day 1 or 2 among +/- hypoglycemia subjects, thus negating any antecedent hypoglycemia or practice effect having an impact on a group effect.

During the testing periods, subjects either drove the simulator or sat in the simulator and watched a videotape of someone else driving a simulator. At 0, 10, 20, and 30 min into testing, subjects rated four autonomic symptoms (sweatiness, pounding heart, jittery/tension, and trembling) and five neuroglycopenic symptoms (uncoordination, visual difficulty, lightheadedness, difficulty concentrating, and confusion) on a 0 (not at all) to 6 (extremely) scale. If subjects believed they were experiencing low blood glucose any time during testing they were instructed to self-treat with an orange drink (sugar-free placebo).

Subjects were told their blood glucose was going to be raised and lowered for testing throughout the study but were kept blind to their actual blood glucose and targeted blood glucose levels. Researchers conducting the testing were kept blind to whether subjects had or did not have a recent history of hypoglycemia-related driving mishaps.

The Atari Research Driving Simulator is an interactive, fixed-platform, virtual

reality simulator that generates reliable, accurate, sensitive, and valid driving performance data (7,8,17–21). The simulator has three 25-inch computer screens that provide a 160° visual field, along with a programmed rearview mirror depicting rear traffic. The driving environment is realistic, incorporating a typical-sized steering wheel, gas and brake pedals, seat, and seat belt. Driving performance feedback is provided visually through the three screens that update at a rate of 60 times/s, audibly through quadraphonic speakers delivering engine, tire, and road noises, and kinesthetically through forced feedback from the steering wheel and pedal pressure. The simulator records three steering variables (SD of lane position, driving off road, and veering across the midline), three braking variables (inappropriate braking while on the open road, missed stopped signals, and collisions), and four speed control variables (exceeding speed limit, SD of speed, time at stop sign deciding when to turn left, and time to execute a left turn).

Outcome variables

With use of the algorithm of DeFronzo et al. (22), an individual's metabolic demand was determined and reported as glucose utilization rates in milligrams per kilogram per minute. Plasma epinephrine was measured using a single isotope derivative method (15).

As in previous studies that discriminated high-risk subjects and predicted future driving collisions (7,8,14,17–21), 32 we generated and analyzed a composite impaired driving score (IDS) to compare the various aspects of driving poorly. To compute the IDS, a subject's performance on each variable (e.g., SD of speed) was converted into a z score based on all subjects' performances on that variable dur-

ing euglycemia and hypoglycemia. The z scores for all variables were then summed for each subject from each test drive, generating the IDS. Thus, an IDS of 0 represents average driving, an IDS < 0 represents better than average driving (e.g., an IDS of –1 represents driving performance 1 SD per variable better than average), and an IDS > 0 represents worse than average driving.

To evaluate whether +history subjects differed from –history subjects across euglycemia and hypoglycemia, two between (group) × two within (conditions) repeated-measures ANCOVAs were performed, with subject's average blood glucose for that condition used as the covariate.

RESULTS

Carbohydrate utilization

+History subjects demonstrated a trend toward greater carbohydrate utilization ($F = 3.064$, $P = 0.089$). +History subjects demonstrated 16.1% greater carbohydrate utilization to maintain euglycemia than –History subjects.

Driving performance

Although +history subjects drove just as well as –history subjects during euglycemia, they demonstrated a marked impairment in performance during progressive hypoglycemia (group × condition $F = 5.0$, $P = 0.03$). As illustrated in Fig. 2, +history subjects' driving performance worsened almost 2.5 SDs from euglycemia to hypoglycemia, whereas –history subjects demonstrated no driving impairment, driving slightly (but not significantly) better during hypoglycemia.

Epinephrine response

Peak epinephrine released was greater during hypoglycemia than during the euglycemic condition (condition $F = 57.35$, $P < 0.0001$), and +history subjects released less epinephrine during hypoglycemia (group × condition $F = 6.05$, $P = 0.02$). However, post hoc analyses of peak epinephrine response during hypoglycemia (sex × group $F = 2.938$, $P = 0.097$) indicates that this reduced epinephrine response by +history subjects was primarily due to women, with mean peak epinephrine levels for male and female –history and male +history subjects of 382, 329, and 316 pg/ml, respectively, but 168 pg/ml for female +history subjects.

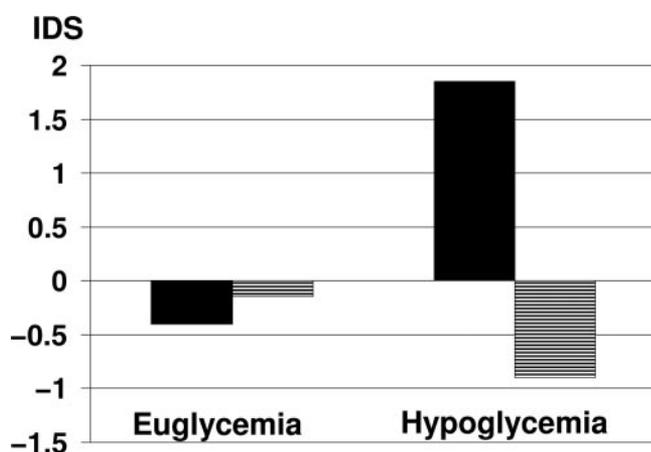


Figure 2—IDS during euglycemic and hypoglycemic conditions for +/−history subjects. ■, +history; ▨, −history.

Symptom perception

+History subjects reported more autonomic symptoms than −history subjects ($F = 7.79$, $P = 0.009$) with a near significant interaction ($F = 3.95$, $P = 0.055$). As seen in Fig. 3, +history subjects tended to report more symptoms during euglycemia than during hypoglycemia, whereas −history subjects demonstrated the anticipated increase in autonomic symptoms during hypoglycemia. Neuroglycopenic symptoms followed a similar pattern: +history subjects tended to report more neuroglycopenic symptoms than −history subjects (group $F = 2.9$, $P = 0.09$), with a significant interaction ($F = 4.00$, $P = 0.05$). Figure 3 illustrates that +history subjects reported more neuroglycopenic symptoms during euglycemia than during hypoglycemia, whereas −history subjects demonstrated the anticipated increase in perceived neuroglycopenic symptoms with hypoglycemia. Contrasts indicated that +history subjects reported more autonomic ($P <$

0.001) and neuroglycopenic ($P = 0.018$) symptoms during euglycemia than −history subjects.

If we assume that hypoglycemic symptom perception in part contributes to self-treatment, self-treatment and symptom perception while driving during hypoglycemia were similar. Both +/−history groups were equally likely to self-treat with the soft drink (44%/59%, respectively, $P = 0.35$) while driving during hypoglycemia.

CONCLUSIONS— This study demonstrated that type 1 diabetic drivers with a history of recurrent hypoglycemia-related driving mishaps during the previous year differed on several basic levels from drivers with no such history. However, it is important to point out that these groups did not differ in terms of general demographic variables (e.g., age, education, and BMI), diabetes parameters (e.g., duration of disease, A1C, insulin regimens, hypoglycemia unawareness, and

long-term complications), or driving parameters (e.g., driving history or miles driven) (Table 1). The exception was that the +history subjects reported three times more episodes of severe hypoglycemia during the previous year.

Although the +history group demonstrated equivalent driving performance during euglycemia, relative to the −history group, their overall driving performance during the 30-min induction of hypoglycemia from 3.9 to 2.5 mmol/l was worse. Our design did not allow us to determine at what blood glucose level this impairment first manifested itself. In contrast, our −history group did not demonstrate a decay.

Drivers with a positive history of mishaps tended to require more infused dextrose to maintain euglycemia during similar insulin challenges, suggesting that these individuals may be more vulnerable to hypoglycemia due to increased glucose utilization. When exposed to progressive mild hypoglycemia, they released less epinephrine, possibly making them more likely to slip into deeper hypoglycemia. Further, when they were experiencing progressive mild hypoglycemia, they demonstrated greater neuroglycopenia as suggested by a significant worsening of driving performance by 2.5 SD.

Drivers with and without a history of hypoglycemia-related driving mishaps did differ significantly in symptom perception during euglycemia but were symptomatically equivalent during progressive hypoglycemia. Detection of autonomic and neuroglycopenic symptoms is a key way for individuals with type 1 diabetes to recognize hypoglycemia during routine functioning (23). Not only did +history drivers fail to detect an increase in symptoms during the induction of hy-

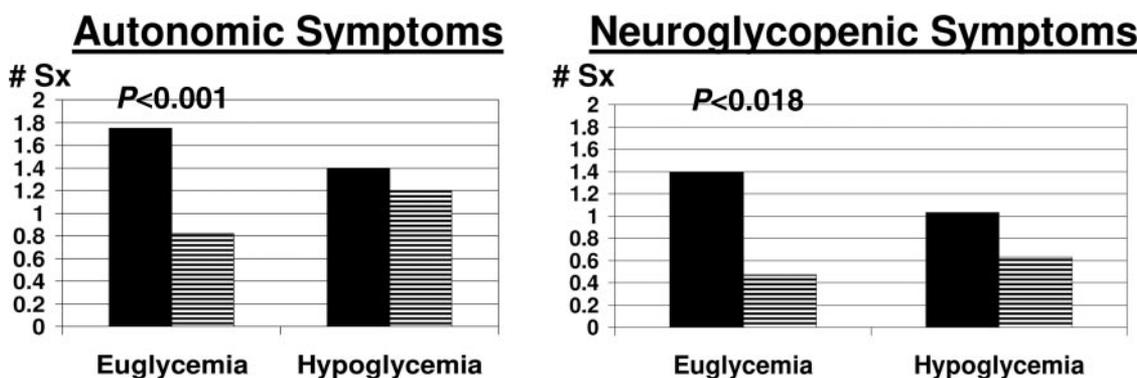


Figure 3—Mean number of significant autonomic and neuroglycopenic symptoms endorsed while driving under euglycemic and hypoglycemic conditions for +/−history subjects, with P levels reflecting differences between groups at euglycemia. ■, +history; ▨, −history. Sx represents the mean number of symptoms.

poglycemia, but they also actually reported more such symptoms during euglycemia than -History drivers. It is as if the former group has to deal with symptom "noise," i.e., a background of symptoms occurring during euglycemia that may make it difficult to detect the "signal" of hypoglycemia, in other words a poor symptom-to-noise ratio. It is not clear from the present study whether this is a general condition for these individuals or if there is something unique to driving that triggers this inversion of symptom perception. Despite these differences in epinephrine release and perceived symptoms, -history (59%) and +history (44%) subjects were similarly likely to self-treat. This may be because self-treatment of hypoglycemia seems to be related to detected difficulties driving and not classic symptoms of hypoglycemia (24). Further, this relatively low rate of self-treatment while hypoglycemic is consistent with the subjects' self-report that they seldom carried fast-acting glucose in their car, along with previously reported data indicating that drivers are willing to drive with low blood glucose (10).

Because a recent history of hypoglycemia-related driving mishaps heralds the likelihood of future driving mishaps (1,3,13), these findings have several clinical implications: Such high-risk drivers 1) may require more robust carbohydrate dosing to prevent or to treat hypoglycemia, 2) should be counseled in terms of an appropriate blood glucose threshold when not to begin driving, e.g., 5 mmol/l, which would vary depending on the length of the drive and whether their blood glucose will be rising or falling during the course of the drive, and 3) should be encouraged to immediately stop driving if blood glucose falls to <4 mmol/l, treat themselves with sufficient fast-acting carbohydrates, and not resume driving until blood glucose is >5 mmol/l.

Limitations of this study should be considered. First, like most insulin clamp studies, these data represent a single observation in a laboratory setting. Therefore, the external validity of these findings cannot be confirmed. Second, this study was partially based on driving a simulator, not an actual car with real-life traffic and driving demands/risks. Third, this was a relatively small sample of only 38 adult drivers with type 1 diabetes. This small sample size may not have had sufficient power to identify small but potentially important differences between these two groups, such as differences in sex

(-history = 34% women as compared with 62% for +history group). Finally, although this crossover design controlled for effects of antecedent hypoglycemia, an alternative design would have been to separate testing days by 2 weeks while rigorously avoiding hypoglycemia for 2 weeks before each testing. However, these limitations are offset by the fact that these a priori findings replicate previous post hoc analyses with an independent sample and different research staff but using similar methodologies and technologies (14). In addition, the simulator used in this study has been found to predict on-road driving behaviors (21) and predict future collisions (20). Given the potential gravity of the consequences of hypoglycemia-related collisions (9), it would seem clinically prudent to use these findings as a guide when working with individuals who are at a higher risk for hypoglycemia while driving, despite these methodological limitations.

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D.J.C. oversaw the project and wrote the manuscript. B.K. conducted data analysis and revised/edited the manuscript. S.M.A. led the inpatient patient management. W.L.C. provided medical oversight for the project. L.A.G.-F. coordinated data collection.

References

1. 1.2 m killed on the road every year [article online], 2006. Available from <http://archive.gulfnews.com/indepth/trafficwatch/Accidents/10028835.html>. Accessed 19 February 2007
2. Songer TJ, Dorsey RR. High risk characteristics for motor vehicle crashes in persons with diabetes by age. *Annu Proc Assoc Adv Automot Med* 2006;50:335–351
3. Cox DJ, Penberthy JK, Zrebiec J, Weinger K, Aikens JE, Frier B, Stetson B, DeGroot M, Trief P, Schaechinger H, Hermanns N, Gonder-Frederick L, Clarke W. Diabetes and driving mishaps: frequency and correlations from a multinational survey. *Diabetes Care* 2003;26:2329–2334
4. Lobmann R, Smid HG, Pottag G, Wagner K, Heinze HJ, Lehnert H. Impairment and recovery of elementary cognitive function induced by hypoglycemia in type-1 diabetic patients and

5. Gold AE, Deary IJ, MacLeod KM, Thomson KJ, Frier BM. Cognitive function during insulin-induced hypoglycemia in humans: short-term cerebral adaptation does not occur. *Psychopharmacology* 1995;119:325–333
6. Gonder-Frederick LA, Cox DJ, Driesen NR, Ryan CM, Clarke WL. Individual differences in neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM. *Diabetes* 1994;43:1407–1412
7. Cox DJ, Gonder-Frederick L, Clarke W. Driving decrements in type 1 diabetes during moderate hypoglycemia. *Diabetes* 1993;42(2):239–243
8. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Julian DM, Clarke WL. Progressive hypoglycemia's impact on driving simulation performance. Occurrence, awareness and correction. *Diabetes Care* 2000;23:163–170
9. Cox DJ, Kovatchev BK, Vandecar K, Gonder-Frederick L, Ritterband R, Clarke W. Hypoglycemia preceding fatal car collisions. *Diabetes Care* 2006;29:467–468
10. Clarke WL, Cox DJ, Gonder-Frederick LA, Kovatchev B. Hypoglycemia and the decision to drive a motor vehicle by persons with diabetes. *JAMA* 1999;282:750–754
11. Weinger K, Kinsley BT, Levy CJ, Bajaj M, Simonson DC, Cox DJ, Ryan CM, Jacobson AM. The perception of safe driving ability during hypoglycemia in patients with type 1 diabetes mellitus. *Am J Med* 1999;107:246–253
12. Cryer PE, Davis SN, Shamon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–1912
13. Cox DJ, Ford D, Gonder-Frederick LA, Clark WL, Mazze R, Weinger K, Ritterband L. Driving mishaps among individuals with type 1 diabetes mellitus: a prospective study. *Diabetes Care* 2009;32:2177–2180
14. Cox DJ, Kovatchev BP, Gonder-Frederick LA, Clarke WL. Physiological and performance differences between drivers with type 1 diabetes mellitus (T1DM) with and without a recent history of driving mishaps: an exploratory study. *Can J Diabetes* 2003;27:23–29
15. Cryer PE, Santiago JV, Shah S. Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright posture. *J Clin Endocrinol Metab* 1974;39:1025–1029
16. Anderson SM, Clarke WL, Cox DJ, Gonder-Frederick LA, Kovatchev BP. Development of a novel glucose clamping technique for steady hypoglycemic descent. *Diabetes* 2004;53:A485
17. Cox DJ, Quillian WC, Thorndike FP, Ko-

- vatchev BP, Hanna G. Evaluating driving performance of outpatients with Alzheimer's disease. *J Am Board Fam Pract* 1998;11:264–271
18. Quillian WC, Cox DJ, Kovatchev BP, Phillips C. The effects of age and alcohol intoxication on simulated driving performance, awareness and self-restraint. *Age Ageing* 1999;28:59–66
 19. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. *Pediatrics* 2006;118:e704–e710
 20. Cox DJ, Broshek DK, Kiernan BP, Kovatchev BP, Guerrier J, Giulano A, George C. Specific driving impairments with progressive age. *Adv Med Psychother Psychodiagn* 2002;11:107–122
 21. Cox DJ, Taylor P, Kovatchev B. Driving simulation performance predicts future accidents among older drivers. *J Am Geriatr Soc* 1999;47:381–382
 22. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214–E223
 23. Gonder-Frederick LA, Cox DJ, Bobbitt SA, Pennebaker JW. Blood glucose symptom beliefs of diabetic patients: accuracy and implications. *Health Psychol* 1986;5:327–341
 24. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Clarke WL. Self-treatment of hypoglycemia while driving. *Diabetes Res Clin Pract* 2001;54:17–26
 25. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–522